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Comparison the Effects of Esomeprazole with the Combination of Esomeprazole and Baclofen in the Treatment of Infantile Gastroesophageal Reflux Disease

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Abstract: Gastro Esophageal Reflux Disease (GERD) is a common and chronic disease in children, especially in children under 2 years old. Proton pump inhibitors (PPIs) have been recommended as the effective therapy in GERD. Esomeprazole is a safe and tolerable PPI in pediatrics. Studies have also shown that Baclofen effectively reduces symptoms of GERD in adult, but there are limited studies in pediatric patients. Purpose: This study aimed to compare the effect of Esomeprazole and the combination of Esomeprazole and Baclofen in the treatment of infantile GERD and its related manifestations. Methods: In a randomized clinical trial study, 50 infants with GERD were selected and randomly assigned into two groups receiving Esomeprazole (1mg/kg, once daily for two weeks) or a combination of Esomeprazole (1mg/kg, once daily for two weeks) and baclofen (0.2 mg/kg, once daily for two weeks). Patients were evaluated for reflux symptoms before treatment as well as at one week, two weeks, four weeks, two months and three months after initiation of treatment. The rate of remission of reflux was also determined in two groups. Results: During three months of treatment, improvement of symptoms associated with reflux including sleep disturbance, refusal to eat, restlessness, impaired quality of life, frequency of waking, nausea and regurgitation in the group treated with Esomeprazole plus baclofen were more favorable than those treated with Esomeprazole alone. Conclusion: Addition of baclofen to Esomeprazole can improve reflux disease more rapidly and favorably in infants with GERD.

Keywords: Gastro Esophageal Reflux Disease, Esomeprazole, Baclofen, Infant

1. Introduction

Gastro Esophageal Reflux Disease (GERD) refers to the passage of contents from the stomach to the esophagus with or without vomiting [1]. Lack of timely treatment of the disease can lead to complications such as reluctance to eat and as a result, stunted growth and even apnea and aspiration pneumonia [2]. GERD has a high prevalence of about 61% in children less than 4 months [3]. Drug treatment of the disease is performed for cases of complicated reflux or to reduce pain and complications caused by the disease [4]. GERD medications include antacids and acid secretion inhibitors medications such as pump proton inhibitors (PPIs) [3]. Esomeprazole is a PPI that reduces stomach acid levels [3], however may be acompained with some side effects such as anxiety, confusion, headache, migraine, chest pain, frequent urination, hyperglycemia, hyperlipidemia, hypertension, and skin rash [5]. Another drug that is sometimes used to treat GERD is baclofen that exerts its effect by inhibiting the transmission of monosynaptic and polysynaptic reflexes at the spinal cord, leading to increased cardiac tonicity [6].

Because reflux in infants may be associated with serious complications such as aspiration of gastric secretions to the

lungs and complications such as infection and even infant death, early treatment is important. Additionally, the effect of drugs used such as antacids and PPIs such as Esomeprazole is relative and the effectiveness of these drugs have been reported differently. Also, the use of these drugs may be associated with side effects in infants. Hence, the aim of this study was to compare the effect of Esomeprazole and the combination of Esomeprazole and Baclofen in the treatment of infantile GERD.

2. Materials and Methods

2.1. Study Population

This study was planned as a clinical trial study with the ethical code IR.MUQ.REC.1398.039 in the ethics committee of Qom University of Medical Sciences and with the clinical trial registration code of IRCT20130311012782N44 in the Iranian Clinical Trial Registration Center. The study was conducted in 2019 in Hazrat Masoumeh Hospital in Qom. The target population included the infants with GERD diagnosed clinically by a pediatrician and based on diagnostic tests for GERD such as ultrasound to detect pyloric stenosis, measure esophageal acidity, esophageal contrast barium, and upper endoscopy. The sample size required for the study was calculated according to the results of the percentage of disease remissionreleased by Khodadad et al. [7], taking into account the type 1 error of 5% and the power of 90%. The data collection tool was a researcher-made data collection form that includes two sections of demographic information (maternal age, gestational age, birth weight, current weight, and distance from cardiac pregnancies) and information on GERD symptoms. All infants were assessed before the intervention as well as one week, two weeks four weeks, two months and three months after the start of treatment for nocturnal restlessness, frequency of waking up at night, regurgitation (return of stomach contents to the infant immediately after feeding), nausea and vomiting, respiratory distress, cough and refusal to feed and the results were recorded in the data collection form of each infant. Weight, height and heart rate of infants were also monitored and recorded during the mentioned time intervals. Regurgitation was considered as the return of stomach contents after infant feeding, which was also reviewed and recorded with a question from the mother.

2.2. Study Intervention

The study participants were randomly (using random allocation software) assigned to treated with Esomeprazole capsules (1 mg/kg once a day for two weeks) (group A) or with a combination of Esomeprazole (1 mg/kg once a day) in addition to baclofen tablets (0.2 mg/kg once a day) for 14 days (group B). For this purpose, chewable tablets of baclofen (digestive) were dissolved in water and given to the infant. The method of blinding was that the drug was prescribed to the patient by the attending physician and the outcome of the intervention was assessed by a pediatrician who was unaware of the type of prescription drug for the infant. The diagnosis of non-weight gain was assessed by the infant growth curve drawn for the child each week, and weight loss or lack of proper weight gain was measured and recorded at each examination. The drugs-related side effects such as palpitations, nystagmus, hypotension, skin rash, rigidity and dystonia were also recorded. Of course, these side effects are all rare and will disappear if occur with discontinuation of the drug, and subsequent examinations of the child will suffice [8]. During the implementation of the plan, the infants were carefully examined for complications by the attending physician.

2.3. Statistical Analysis

The obtained data were finally entered into SPSS software version 25 and and analyzed with Chi-square test (to compare qualitative and nominal data of the two groups), or T-test (to compare quantitative data between the two groups). The Repeated Measure ANOVA test was also employed to compare the trend of changes in variables within and between groups.

3. Results

In this study, 68 infants with GERD were studied that 50 eligible patients were finally selected and assigned in the two groups receiving Esomeprazole alone or Esomeprazole plus Baclofen combination (Figure 1). There was no significant difference between the two groups in terms baseline characteristics including demographics, mean maternal age, gestational age, birth weight, current weight and time between pregnancies (Table 1).

Table 1. *Baseline characteristics of study subjects.*

Characteristics	Baclofen+Esomeprazole (n = 25)	Esomeprazole alone (n = 25)	P value
Mean age, month	5.82±2.15	6.12±2.11	0.62
Mean age of mother	28.36±4.55	29.48±4.97	0.41
Mean gestation age	38.28±0.74	38.28±0.61	0.99
Mean birth weight	3106.0±228.36	3146.0±247.87	0.57
Mean current weight	6948±1580	7436±1065	0.21
Time interval between pregnancies	1.92±1.5	2.04±2.03	0.81
Male neonate gender	14 (56.0)	13 (52.0)	0.78

Results are presented as mean±SD or number (percentage)
P value < 0.05 as the significant
No difference was revealed between the two groups in baseline characteristics.

Figures 2 to 4 show the trend of the changes in neonatal weight, height, and heart rate before intervention until 3 months after treatment. According to the mentioned results, the weight of infants increased by 25.39±8.14% in Esomeprazole+baclofen group and 18.24±8.24% in those were treated with Esomeprazole indicating no difference (P = 0.35). The percentage of magnitude changes in the two groups were 1.68 ± 7.3 and 5.9 ± 7.9%, respectively, without any difference between the two groups (P = 0.14). However, the percentage of heart rate changes was significantly different between the two groups (P = 0.011), so that in the group receivingEsomeprazole+baclofen group it was found to be 7.1 ± 6.9 and in those receivingEsomeprazole alone was 5.11 ± 5.1%. According to Table 2, some of the signs and symptoms of GERD, including wheezing, ear infection, cough, and hiccups, improved in all patients in both groups within a week of starting treatment, while by the end of treatment, none of these symptoms were seen in patients. According to Table 3, other symptoms associated with GERD include sleep disturbance, apnea, refusal to eat, vomiting, excessive crying, sleep disturbance, nausea, and regurgitation during treatment were all improved in the Esomeprazole+baclofen-treated group, while in the group receiving Esomeprazole alone, the prevalence of these symptoms decreased but no improvement was revealed in all patients. The mean number of awakenings before the intervention was not significantly different between the two groups, but at other times, the difference between the two groups was significant that the group treated with S omeprazole+baclofen woke up less frequently at night.

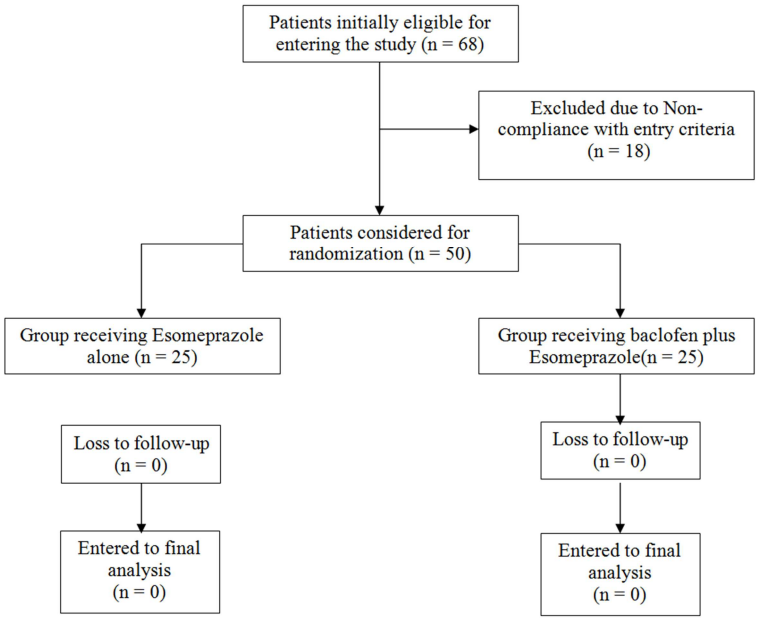

Figure 1. *The flowchart of selecting the patients for trial.*

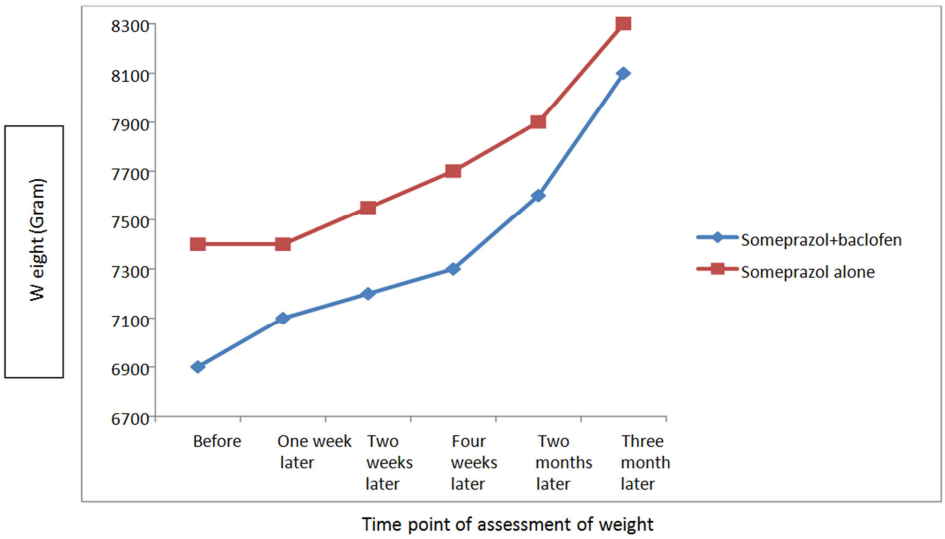

Figure 2. *The trend of the changes in weight (Significant trend of the changes was revealed in body weight between the groups receiving Baclofen+Esomeprazole and Esomeprazole alone).*

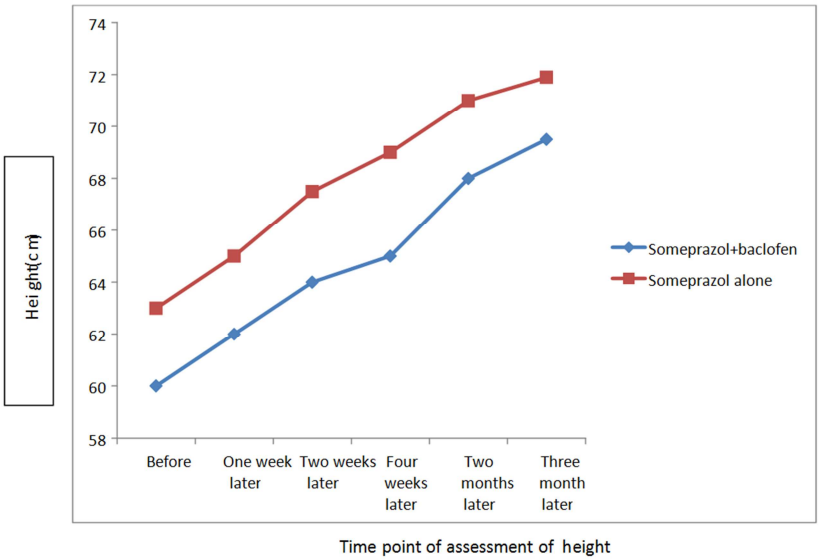

Figure 3. *The trend of the changes in height (Significant trend of the changes was revealed in body height between the groups receiving Baclofen+Esomeprazole and Esomeprazole alone).*

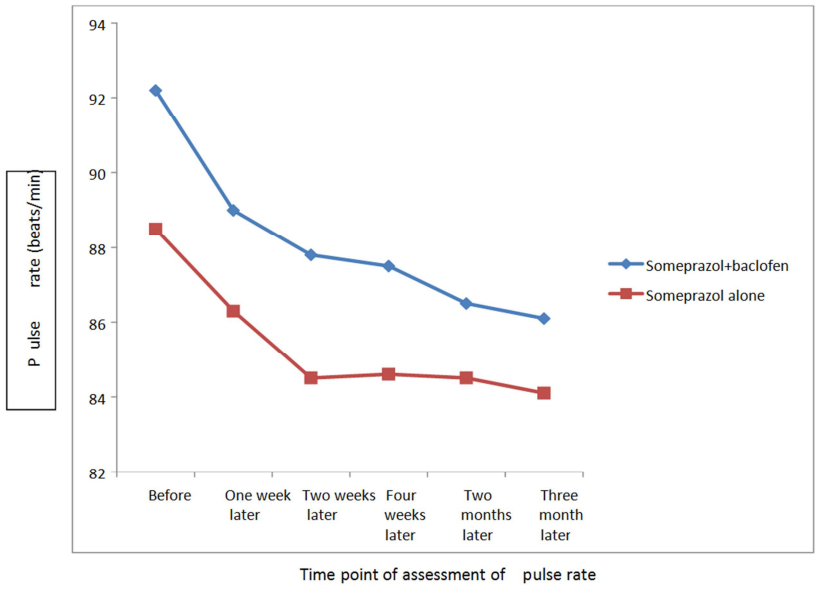

Figure 4. *The trend of the changes in pulse rate (Significant trend of the changes was revealed in pulse rate between the groups receiving Baclofen+Esomeprazole and Esomeprazole alone).*

Table 2. *Distribution of wheezing, otitis media, cough and hiccups during the intervention.*

Characteristics	Baclofen+Esomeprazole (n = 25)	Esomeprazole alone (n = 25)	P value
Wheezing			
Before	25 (100)	21 (84.0)	0.11
One week later	4 (16.0)	3 (12.0)	0.99
Otitis media			
Before	4 (16.0)	14 (56.0)	0.003
One week later	1 (4.0)	1 (4.0)	1.000
Cough			
Before	19 (76.0)	21 (84.0)	0.48
One week later	1 (4.0)	2 (8.0)	0.99
Hiccups			
Before	1 (4.0)	0 (0.0)	0.99
One week later	2 (8.0)	0 (0.0)	0.49

Results are presented as mean±SD or number (percentage)
P value < 0.05 as the significant
There was no difference between the two groups in wheezing, otitis media, cough and hiccups one week after intervention.

Table 3. *Distribution of sleep disorders during the intervention.*

Characteristics	Baclofen+Esomeprazole (n = 25)	Esomeprazole alone (n = 25)	P value
Sleep problem			
Before	24 (96)	24 (96)	1.000
One week later	5 (20)	20 (80)	<0.001
Two weeks later	0 (0)	18 (72)	<0.001
Four weeks later	0 (0)	16 (64)	<0.001
Two months later	0 (0)	12 (48)	<0.001
Three month later	0 (0)	10 (40)	<0.001
Apnea			
Before	24 (96)	24 (96)	1.000
One week later	5 (20)	20 (80)	<0.001
Two weeks later	0 (0)	18 (72)	<0.001
Four weeks later	0 (0)	16 (64)	<0.001
Two months later	0 (0)	12 (48)	<0.001
Three month later	0 (0)	10 (40)	<0.001
Refusal to eat			
Before	24 (96)	25 (100)	0.99
One week later	5 (20)	25 (100)	<0.001
Two weeks later	3 (12)	25 (100)	<0.001
Four weeks later	1 (4)	25 (100)	<0.001
Two months later	0 (0)	25 (100)	<0.001
Three month later	0 (0)	25 (100)	<0.001
Vomiting			
Before	24 (96)	25 (100)	0.99
One week later	18 (72)	16 (64)	0.54
Two weeks later	4 (16)	9 (36)	0.11
Four weeks later	1 (4)	8 (32)	0.023
Two months later	0 (0)	6 (24)	0.022
Three month later	0 (0)	4 (16)	0.11
Cry too much			
Before	25 (100)	25 (100)	1.000
One week later	4 (16)	24 (96)	<0.001
Two weeks later	1 (4)	21 (84)	<0.001
Four weeks later	1 (4)	19 (76)	<0.001
Two months later	0 (0)	16 (64)	<0.001
Three month later	0 (0)	17 (68)	<0.001

Results are presented as mean±SD or number (percentage)

P value < 0.05 as the significant

There was higher rate of improvement in Sleep problem, Apnea, Refusal to eat, and Cry too much in patients receiving Baclofen+Esomeprazole three months after intervention.

Table 3. *Continued.*

Characteristics	Baclofen+Esomeprazole (n = 25)	Esomeprazole alone (n = 25)	P value
Sleep quality dis.			
Before	23 (92)	25 (100)	0.99
One week later	5 (20)	24 (96)	<0.001
Two weeks later	1 (4)	21 (84)	<0.001
Four weeks later	0 (0)	19 (76)	<0.001
Two months later	0 (0)	18 (72)	<0.001
Three month later	0 (0)	17 (68)	<0.001
Nausea			
Before	25 (100)	24 (96)	0.99
One week later	21 (84)	25 (100)	0.11
Two weeks later	8 (32)	25 (100)	<0.001
Four weeks later	1 (4)	23 (92)	<0.001
Two months later	0 (0)	22 (88)	<0.001
Three month later	0 (0)	17 (68)	<0.001
Regusrigation			
Before	25 (100)	25 (100)	1.000
One week later	25 (100)	25 (100)	1.000
Two weeks later	25 (100)	25 (100)	1.000
Four weeks later	13 (52)	24 (96)	<0.001
Two months later	7 (28)	23 (92)	<0.001
Three month later	4 (16)	19 (76)	<0.001
Average frequency of waking up			

Characteristics	Baclofen+Esomeprazole (n = 25)	Esomeprazole alone (n = 25)	P value
Before	3.00±1.0	2.60±1.0	0.25
One week later	1.40±0.8	2.00±0.9	0.032
Two weeks later	0.40±0.5	1.60±0.9	<0.001
Four weeks later	0.24±0.5	1.30±0.9	<0.001
Two months later	0.24±0.7	1.10±0.9	<0.001
Three month later	0.20±0.5	1.00±0.8	<0.001

Results are presented as mean±SD or number (percentage)
P value < 0.05 as the significant
There was higher rate of improvement in Sleep quality, Nausea, Regusrigation, and Average frequency of waking up in patients receiving Baclofen+Esomeprazole three months after intervention.

4. Discussion

Preliminary results of the study showed that the two groups were not significantly different in terms of the distribution of demographic and general variables including age distribution, birth weight, gestational age, and weight at the time of admission and the distance between births and previous pregnancies and thus the conflunding effects of such parameters were refused.

Examination of changes in weight and height of infants during the three-month period of GERD showed that changes in weight and height in both groups increased and in fact, no significant difference was seen between the two groups in terms of changes in weight and height. Although the results of several studies show that reflux treatment leads to improved weight gain [9], but in our study, because there was no control group and both groups were treated for reflux, weight and height changes between the two groupsremained insignificant. On the other hand, due to the diagnosis of GERD in the infants under study, it was not ethically possible to use methods such as placebo. In fact, the results of this section show that adding baclofen to Esomeprazole does not have a significant effect on gaining more weight and increasing the height of infants. In addition, according to the results of our study, none of the infants in the study experienced intrauterine growth retardation or growth retardation at birth (according to the Health Center). In this regard, the results of the study of Khodadad et al showed a significant difference in the average weight gain within months after treatment by usingPPIs (p <0.0001). According to this research, baclofen is able to control volumetric reflux attacks. Finally, it is effective in weight gain and improving the nutritional status of infants [8]. While in our study, weight gain was observed in both groups during the three months after the start of treatment and there was no significant difference between the two groups.

Examination of vital signs of infants during the study period including pulse changes showed that reflux treatment protocols in both groups were associated with significant changes in pulse rate but the rate of changes in the group treated with Esomeprazole +baclofen was greater and patients in this group during treatment had a higher mean pulse rate. In this regard, studies have shown that baclofen can increase heart rate [7], and the differences between the two groups are probably related to the side effects of baclofen in infants. However, due to the low dose of baclofen and the absence of serious side effects in shortness of breath, it is possible to rely on the safety of this drug in infants with the recommended dose [10].

Sleep disorders (the frequency of waking up at night) were among the problems that had a high prevalence in both groups before the intervention, but during treatment, its prevalence was significantly reduced. On the other hand, the number of awakenings at night was significantly higher in the group treated with Esomeprazole+Baclofen. Therefore, it can be concluded that co-administration of baclofen with S omeprazole can be effective in improving the sleep of infants with GERD. In a study by Vela et al, it was also mentioned that the administration of baclofen in infants with GERD improves the sleep quality of infants [11]. Persistent nausea, insomnia, lack of sleep, and frequent awakenings are other problems for infants with GERD that severely affect the infant's health, and reflux treatment improves these symptoms. The results of our study showed that the addition of baclofen to Esomeprazole has a more favorable effect on improving sleep quality, relieving the symptoms of insomnia and the frequency of waking up.

According to the findings of our study, one week after the start of treatment, the rate of wheezing and middle ear infection in both groups was zero and by the end of the study, no case of these complications was seen in patients in both groups. Coughing, wheezing, and lung infection are common problems in infants with GERD due to food returning from the esophagus to the throat and entering the respiratory tract [2], which can eventually lead to pneumonia [3]. The results of a study conducted by Berquist et al showed that more than 60% of infants with GERD develop lung infection and GERD treatment reduces the risk of respiratory tract infections, especially aspiration pneumonia [12].

According to the results of the present study, the incidence of ear infections in all patients was significantly reduced and two weeks after the start of treatment until the end of the third month, no case of ear infection was seen in infants of the two groups. A study by Tasker et al in 2002 found that a high percentage of infants with GERD had ear infections, and that reflux treatment in infants resulted in a significant reduction in the incidence of otitis media in these patients [13].

The results of our study showed that the use of Esomeprazole+baclofen had a more favorable effect on the elimination of the symptom of refusal of nutrition, so that

one month after the start of treatment, all patients treated with Esomeprazole+baclofen did not refuse to eat. However, all patients treated with Esomeprazole alone, from the beginning to the end of the study, had no withdrawal symptoms and no improvement was seen in patients in this group. The results of Khodadad et al study have also shown that baclofen treatment improves the nutritional status of infants with GERD [7], which are consistent with the results of our study. On the other hand, a high prevalence of malnutrition in infants with GERD has also been reported in Orenstein [2] and Vandenplas [14] studies.

According to the results of our study, the reduction of nausea and vomiting in the group treated with Esomeprazole+baclofen was more than the group treated with S-omeprazole alone, and therefore it seems that the use of baclofen in the treatment of GERD can relieve nausea and vomiting in infants is beneficial and effective. The results of a study conducted by Vadlamudi et al also showed that the use of baclofen in the treatment of infantile reflux leads to the elimination of symptoms such as recurrent nausea and vomiting [15].

According to the findings of our study, all mothers of infants in the study complained of excessive crying of their infants, but in one month after reflux treatment, according to mothers, no case of excessive infant crying was reported in the group treated with Esomeprazole+baclofen, while the reduction of this symptom in the group treated with Esomeprazole alone was not significant, and in general, the use of baclofen with Esomeprazole had a more favorable effect on relieving excessive crying in infants. Excessive crying is one of the symptoms that can occur in infants due to the effects of food returning to the esophagus and symptoms such as chest burning, which are caused by excessive crying in infants [4].

The results of our study showed that before starting treatment, all infants had symptoms of regurgitation, but during the three months of the intervention, the prevalence of this symptom decreased in both groups, but the rate of reduction in the group treated with Esomeprazole+baclofen was significantly more. In two studies by Koek and Van, adding baclofen to GERD regimen was associated with a significant reduction in regurgitation [16, 17].

5. Conclusion

The findings of our study showed that the addition of baclofen to Esomeprazole improved symptoms more quickly and rapidly than Esomeprazole alone in infants with GERD. There are limited studies on the therapeutic effects of baclofen in infants and children. Investigating the effectiveness of different doses of baclofen in a larger statistical population can have more accurate results.

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